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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,006	04/27/2001	Hansgeorg Schindler	SONN:010US/MBW	1473

7590 07/06/2007  
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EXAMINER
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EPPERSON, JON D

ART UNIT	PAPER NUMBER
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1639

MAIL DATE	DELIVERY MODE
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07/06/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

09/845,006

Applicant(s)

SCHINDLER, HANSGEORG

Examiner

Jon D. Epperson

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1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 02 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 24, 26-45 and 61-68 is/are pending in the application.
- 4a) Of the above claim(s) 41 and 43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 24, 26-40, 42, 44, 45, 61, 62, and 65-68 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date: \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_.

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## **DETAILED ACTION**

### ***Status of the Application***

1. The Response filed April 2, 2007 is acknowledged.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

### ***Status of the Claims***

3. Claims 24, 26-45, 61 and 62 were pending. Applicants added claims 63-68. No claims were amended or canceled. Therefore, claims 24, 26-45, and 61-68 are currently pending. Claims 41 and 43 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim.
4. Therefore, claims 24, 26-40, 42, 44, 45, and 61-68 are examined in this action.

### **Withdrawn Objections/Rejections**

5. The New Matter rejection under 35 U.S.C. § 112, first paragraph is withdrawn in view of Applicants' arguments (e.g., see 12/22/06 Response, pages 8 and 9). All other rejections are maintained and the arguments are addressed below.

### **Outstanding Objections and/or Rejections**

***Claims Rejections - 35 U.S.C. 112, second paragraph***

6. Claims 24, 26-40, 42, 44, 45, 61, 62, and 65-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

AA. Withdrawn.

BB. ***Claims 24, 65, 67, and 60*** recite “large-area” fluorescence excitation. The term “large-area” is a relative term, which renders the claim indefinite and/or unclear. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. See also MPEP § 2173.05(b). The Examiner notes that Applicant’s specification states, “Due to the large-area fluorescence excitation, preferably 100 to 10,000  $\mu\text{m}^2$ , depending on the application, imaging of the excited molecules may be very rapid” (see page 7, paragraph 2). However, this statement is merely exemplary in nature and does not further limit the term “large” to a range from 100 to 10,000  $\mu\text{m}^2$  and, as a result, it is not clear to what extent the term “large” could extend beyond this limit (e.g., would 90  $\mu\text{m}^2$  infringe, 80  $\mu\text{m}^2$  infringe, etc). Thus, the metes and bounds of the claimed invention cannot be determined. Therefore, claim 24, 65, 67, 68 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

CC. For **claim 62**, the phrase “wherein the arrangement is adapted to visualize movements of molecules ... by using the single dye tracing (SDT) method” is vague and indefinite. For example, the claimed recitation of a use (i.e., “use” of the SDT method), without setting forth any steps involved in the process (i.e., no positive method steps are

set forth for the SDT method in the claim), results in an improper definition of a process (e.g., see for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966)) and, as a result, an improper definition of the apparatus that is defined (in part) by said process. Furthermore, it would appear that all of the recited elements (e.g., source of light, sample holder, etc.) could be used to monitor the movement of molecules, interactions between molecules, etc. without such an adaptation (e.g., see claim 1 of PCT/AT99/00257 priority document wherein no such “adaptation” is required for “visualizing molecules, movements thereof, and interactions between molecules, and molecular processes in a sample, in particular molecules and processes in biological cells, by using the single dye tracing”; see also specification pages 6-7). Thus, it is not clear what adaptation would be required when Applicant’s priority document and specification states that no such adaptation is required.

In addition, the Schmidt et al. reference (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. “Imaging of single molecule diffusion” PNAS 1996, 93, 2926-2929) used in the 35 U.S.C. § 103(a) rejection above, according to Applicant, teaches at least one variation of the currently claimed “single dye tracing” method (e.g., see Schmidt, T. H.; Hinterdorfer, P.; Schindler, H. “Microscopy for Recognition of Individual Biomolecules” *Microscopy Research and Technique* **1999**, 44, 339-346, page 339, column 2, “(SDT) permits the detection and imaging of the mobility of individual biomolecules on biological membranes ... Schmidt et al. (1996a) [i.e., Applicant references the above PNAS article, used in the 35 U.S.C. §103(a) rejection as

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an example of an SDT method]”). However, Applicant also states that this SDT method does not lead to the currently claimed “visualization of movements of molecules ...” (e.g., 6/27/05 Response, page 17, paragraph 1, “Schmidt [i.e., the PNAS reference above] does not teach the visualization of movements of molecules ...”). Thus, it is also unclear how the SDT method can be “used” to adapt the currently claimed arrangement for the “visualization of molecules ...” when Applicant expressly acknowledges that the SDT methods does not lead to such a result. Therefore, claim 24 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

### *Response*

7. Applicant’s arguments directed to the above 35 U.S.C. 112, second paragraph rejections denoted BB and CC (formerly denoted A) were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons.

[BB1] Applicant argues, The term "large-area fluorescent excitation" is not indefinite. In its previous Responses, Applicant presented sufficient evidence, including two declarations from a person of ordinary skill in the art, to establish that the term ‘large-area fluorescent excitation' is well-understood by persons of ordinary skill in the art to be synonymous with the term "wide-field illumination," ... The Office contends that Applicant's evidence is insufficient, in part, because none of the three references cited in the Supplemental Sonnleitner Declaration specifically uses the term ‘large-area fluorescent excitation,’ ... [However,] Applicant respectfully notes that the ultimate question in this rejection is whether, in the art of fluorescence microscopy, "large-area" is

a relative term when it is used to modify fluorescence excitation. The references cited by Dr. Sonnleitner are instructive on this question, as they all involve use of the phrase 'large-area' in the context of fluorescent excitation. As explained in Applicant's previous Responses ... 'large-area' is used to distinguish the light source used in non-confocal microscopy (i. e., wide field microscopy) from the light source used in confocal microscopy (in which illumination is performed pixel-wise, i.e., on a spot, rather than over a "large area" or "wide-field")." (e.g., see 12/22/06 Response, page 10).

[BB1] The Examiner respectfully disagrees. As noted previously, the cited references do not mention the term. Thus, the references cannot be relied on as a definition for the term. In addition, the Examiner sets forth Yelen et al. for the sole purpose of rebutting this argument (Yelin et al., "Large area confocal microscopy" Optics Letters, May 1, 2007, 32(9), pages 1104), which proves that "large area" does not refer to the type of technique (i.e., cofoncal, non-confocal) as purported by Applicants (e.g., see 4/10/06 Declaration, page 2, note 3, "'large-area fluorescent excitation' is a completely different technique than confocal microscopy") but, rather, the "dimension" of the sample that is being illuminated (e.g., see Yelin et al., title and abstract wherein confocal microscopy was used to analyze "large area" samples; see also page 1102, column 2, paragraph 2 wherein SECM was demonstrated to have a  $440\text{ }\mu\text{m} \times 400\text{ }\mu\text{m}$  field of view, which compares favorable to Applicants' 100 to 10,000  $\mu\text{m}^2$  example; note also Li et al., which was discussed in the previous office action, wherein a "tiling" procedure was used to examine larger areas). Thus, large field does not describe a technique but, rather, the illumination area. Thus, Applicants' declaration only serves to further prove that the

term is ambiguous. For example, in addition to not knowing what the size is (i.e., “large area” is a relative term), it’s also unclear to what extent this term limits the scope to a particular technique (i.e., whether the term should be limited to non-confocal microscopy as Applicants contend or not). “Claims do not comply with 35 U.S.C. 112 where term therein has more than one definition, with infringement depending on which definition is used.” (e.g., see *Maurice A. Garebell, Inc., et al. v. The Boeing Company et al.*, 180 USPQ 294)

In addition, Applicants’ statement that large area fluorescent excitation is “synonymous” with wide-field illumination is not consistent with the plain text of the claims. For example, Applicants added claim 63 wherein they replaced “large area” with the “wide field” limitation, which is inconsistent with the two terms being synonymous. The doctrine of claim differentiation creates a presumption that each claim in a patent has a different scope. *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998). “There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant.” *Id.* at 1005. Here, claim 63 would be superfluous relative to claim 24 if Applicants’ statement that “large area fluorescent excitation” and “wide field illumination” are synonymous was true.

[BB2] Applicants argue, “While they do not use the exact term ‘large-area



fluorescent excitation,' the references cited by Dr. Sonnleitner are instructive on the definiteness question. They establish that those of skill in the art of fluorescence microscopy frequently use the terms "large area" and "wide-field" not in a relative sense but rather to describe the illumination or fluorescent excitation of samples in a non-confocal manner." (e.g., see 12/22/06 Response, page 11, paragraph 1).

[BB2] See section [BB1] above.

[BB3] Applicants argue, "Applicant respectfully notes that the Office's characterization of the teachings of Li is incorrect. As Li establishes, in wide-field microscopy (i.e., large-area fluorescent excitation), "the entire field of view is uniformly illuminated and observed." Li, p. 2. Conversely, in confocal microscopy, "both the illumination and the detection are confined to a diffraction limited spot." Id. Thus, as Li establishes, in confocal imaging only a "spot" (as opposed to a "large area" or a "wide-field") is illuminated at a given point in time." (e.g., see 12/22/06 Response, page 11, paragraph 2).

[BB3] The examiner respectfully disagrees. The cited passages states that "wide-field" microscopy provides uniform illumination to the "entire field of view," not large-area-fluoresce excitation as purported. Furthermore, this section is entitled "Wide-field of view Confocal Microscopy", not "Wide-field of view non-confocal microscopy" that would otherwise be more supportive of Applicants' position. In addition, the passages states that confocal microscopy can illuminate large areas by either (1) a tiling procedure or (2) the use of a single scan (e.g., see "The wide field-of-view confocal

imaging system ... is capable of confocal imaging of large area specimen in a single scan ... without tiling”).

[BB4] Applicants argue, “A person of ordinary skill in the art would not understand from this disclosure that "large areas" can be excited (i.e., illuminated) using confocal imaging. By definition, in confocal imaging, illumination is performed pixel-wise, i.e., on a spot, rather than over a "large area" or "widefield." The fact that the technique of Li is capable of imaging a "large area in a single scan" does not mean that illumination in Li's technique is not confined to a diffraction-limited spot. If that were true, the technique of Li would not be referred to therein as a "confocal" imaging technique. In describing its confocal system, Li confirms that its technique involves the illumination of a spot rather than a large area: "The raster scan of the focused laser spot across the specimen is realized by scanning in the X (lateral direction) and stage scanning in the Y (longitudinal) direction of the specimen” (e.g., see 12/22/06 Response, paragraph bridging pages 11 and 12).

[BB4] The mechanism by which the “large areas” are excited in Li et al. is not material. This does not change the fact that confocal microscopy was used to image a “large area.” Thus, a person of skill in the art would not limit “large area fluorescent excitation” to confocal microscopy because the term does not suggest that the excitation has to occur all at the same time. Furthermore, even if, assuming arguendo, excitation does have to occur at the same time (i.e., image acquired without tiling<sup>o</sup>) then both Li and Yelin provide evidence that confocal microscopy can be used for this purpose

(e.g., see Yelin et al., page 1102, column 2, paragraph 2, “SECM was previously demonstrated with a  $440\text{ }\mu\text{m} \times 400\text{ }\mu\text{m}$  field of view”; see also Li et al., section 1.3, “The wide field-of-view confocal imaging system presented in this paper\* is capable of confocal imaging of large area specimen in a single scan, e.g., imaging an entire standard microscope slide (1 by 3 inches in size) without tiling”).

[CC1] Applicants argue that the term “use” and “utilizing” are synonyms and, as are result, the reasoning in *In re Porter* applies (e.g., see 12/22/06 Response, page 12).

[CC1] The terms are not the same. The term “for use” implies some future “intended” use whereas the term “utilizing” constitutes a “current” use. In any event, as stated previously, MPEP § 2173.05(q) makes clear that an attempt to claim a method without setting forth positive method steps should be rejected under 35 U.S.C. 112, second paragraph (e.g., see MPEP 5.2173.05(q), “Attempts to claim a process without setting forth any steps involved in the process generally raises an issue of indefiniteness under 35 U.S.C. 112, second paragraph.”). Consequently, any product or apparatus that is described, at least in part, by an indefinite method should also be rejected.

Furthermore, as stated previously, Porter made clear that a “nozzle” was being used/utilized in the method. In contrast, no such tangible object can be perceived here. Thus, even if, assuming arguendo, the terms use and utilized could be interchanged, the result would be the same. For example, Applicants’ specification “defines” the single dye tracing method to comprise:

at least one source of light for large-area fluorescence excitation via single or multi-photon

- absorption by equal or different marker molecules on molecules in the sample,
- a sample holding means for accommodating the sample,
- a highly-sensitive detection and analysis system comprising a charged coupled device (CCD) camera, the sample or the sample holding means, respectively, and/or the detection and analysis system being shiftable relative to each other during the measuring process, and
- a control unit for coordinating and synchronizing illumination times and, optionally, wave lengths of the lateral or vertical movement of the sample or of the sample holding means, respectively, with the sample as well as, optionally, the positioning and shifting of the images of each sample position of the pixel array of the CCD camera.

(see original abstract; see also paragraph 9 where the term is briefly mentioned; see also paragraphs 15-19 wherein the language set forth in the abstract is repeated; see also original claim 1 wherein the same language is repeated; see also original claim 13 wherein the term is briefly mentioned for the last time in the context of biological cells). Thus, the only tangible items that could be used to define the method (like the nozzle in Porter) would be (1) at least one light source for large-area fluorescence excitation, (2) a sample holding means, (3) a highly-sensitive detection and analysis system comprising CCD camera, which is shiftable relative to the sample holding means, and (4) a control unit for coordinating and synchronizing illumination times. The control unit need not control wavelengths of the lateral or vertical movement of the sample or th of the sample holding means because this is an “optional” feature. Likewise, positioning and shifting of the images of each sample position of the pixel array of the CCD camera is also optional. However, none of the elements (1)-(4) mentioned above can constitute the adaptation. For example, claim 24, from which claim 62 depends already recites all of the elements (e.g., see claim 24, lines 2-3 wherein (1) a light source for large-area fluorescence excitation is disclosed; see also lines 4 wherein (2) a sample holding means

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is disclosed; see also lines 5-7 wherein (3) a detection and analysis system is disclosed; see also line 8-10 wherein (4) a control unit is disclosed). Furthermore, although claim 24 does not recite the use of a “highly sensitive” detector as set forth in the original abstract, which might otherwise constitute the adaptation (i.e., sensitive → highly sensitive), the term “highly sensitive” is again a relative term that would render this boundary unclear. In addition, the meaning of the term “highly sensitive” could not be gleaned from the molecules that are observed because the size and intensity of the molecules is not indicated. That is, molecules like those disclosed by Gensch et al. (e.g., see Gensch et al., “Fluorescence Detection from Single Dendrimers with Multiple Chromophores” *Angew. Chem. Int. Ed.* 1999, 38(24), 3752-3756, see entire document, especially, figure 2 and Experimental section), for example, do not require the use of “highly sensitive” equipment (e.g., see figure 2 and Experimental section wherein a unmodified commercially available confocal fluorescence microscope was used to image single molecules). Thus, Applicant’s single-dye tracing method does not disclose the use/utilization of any tangible object like the nozzle in *Porter* and thus this case is not applicable or, alternatively, supports the opposite conclusion set forth by Applicants. It should also be noted that Applicants have not set forth any citations to the specification (page and line number) that would support their position.

[CC2] Applicants argue that the Examiner has again misinterpreted their statements stating, “Applicant never ‘admitted’ that SDT methods could not be used to visualize movements of molecules, interactions between molecules, and molecular processes in a sample.” (e.g., see 12/22/06 Response, page 13, paragraph 1).

[CC2] Even if, assuming arguendo, Applicants didn't make this admission, the claim language would still be indefinite for the reasons set forth in section [CC1].

***Claims Rejections - 35 U.S.C. 102***

8. Claims 24, 26-28, 30-34, 61, 62, 64, and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Sharonov et al. (Sharonov, S.; Chourpa, I.; Morjani, H.; Nabiev, I.; Manfait, M. "Confocal spectral imaging analysis in studies of the spatial distribution of antitumor drugs within living cancer cells" *Analytica Chimica Acta* **1994**, 290, 40-47) (of record).

For **claims 24, 61 and 62**, Sharonov et al. (see entire document) disclose an apparatus for confocal spectral imaging analysis (e.g., see Sharonov et al, abstract; see also figure 2), which anticipates claims 24 and 61. For example, Sharonov et al. disclose at least one source of light adapted to fluorescently excite, via single or multiple photon absorption marker molecules in said sample (e.g., see figure 2, element 1 wherein a Spectra-Physics Model 2026 laser is disclosed as the light source; see also abstract wherein both bound and unbound doxorubicin and mitroxastrone are disclosed and the marker molecules inside the K562 cancer cells; see also figures 4-5). Sharonov et al. do not explicitly state that the light source is configured for use in large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claim 34) (emphasis added). Moreover, Sharonov et al. disclose the excitation of a  $20 \times 20 \mu\text{m}$  region =  $400 \mu\text{m}^2$  (e.g., see Sharonov et al., page 42, column

1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000  $\mu\text{m}^2$  (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000  $\mu\text{m}^2$ , depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection above), which is between 100 to 10,000  $\mu\text{m}^2$ . "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection above).

In addition, Sharonov et al. disclose a sample holder (e.g., see figure 2, element 5). Sharonov et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 2, element 8). Sharonov et al. also disclose a detection and analysis system and a sample holder that are movable laterally relative to each other during use (e.g., see figure 2, elements 2 and 6; see also page 42, last paragraph, "The sample compartment is moved with an automatic scanning stage ... and can be scanned along the y-axis [i.e., laterally] with a minimum step size of 0.1  $\mu\text{m}$ . The scanning of the sample along the x-axis is achieved by the optical scanner being installed in the confocal entrance chamber"). Sharonov et al. also disclose a control unit that is adapted to coordinate and synchronize illumination times and lateral movement

between said sample holder and said detection and analysis system (e.g., see figure 2, elements 6 and 9; see also page 42, column 1, paragraph 2 wherein an IBM PC/AT-486 is disclosed, "The scanning of the sample stage and mirrors of the optical scanner and all operations connected with recording of spectra are computer-controlled (IBM PC/AT-486) by the ImageSoft software through the net-work between the IBM PC/AT and the RISC 6000 work station"; see also page 42, column 2, paragraphs 2-5; see also figure 3).

Sharonov et al. do not explicitly state that said arrangement has been "adapted" to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method. However, the Examiner contends that Sharonov et al. inherently discloses this limitation (e.g., see Sharonov et al., abstract and figure 4). For example, the experimental set up in Sharonov et al. was "adapted" to visualize living cancer cells treated with the fluorescent antitumour drugs doxorubicin and mitroxitron (e.g., see abstract). Thus, Sharonov et al. teach visualization of the movements of molecules (e.g., see Sharonov et al., page 47, "Direct express imaging of drug deposits within cells will be helpful in analyzing the accumulation [i.e., movement], distribution and efflux of the drugs"), interactions between molecules (e.g., see Sharonov et al., page, 44, paragraph bridging columns 1-2, "The fluorescence spectrum of the drug-DNA complex is changed as compared with the free drug") and molecular process in a sample during use (e.g., see page 44, paragraph bridging columns 1-2, see also figures 3-5). Furthermore, Sharonov et al. disclose the use of a "single dye" such as mitroxitron (e.g., see figure 4) or doxorubicin (e.g., see figure 5) in each experiment. "When the PTO shows a sound basis for believing that the



products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term “large-area” fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, the Examiner argues in the alternative that Applicants’ “adaptation” element (i.e., see claim 24, last three lines) represents “intended use” language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). “[A]pparatus claims cover what a device is, not what a device does.” *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A claim containing a “recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus” if the prior art apparatus teaches all the structural limitations of the claim. *Ex parte Masham*, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant’s claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo*

this “adaptation” is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph above).

For **claim 25**, Sharonov et al. disclose an apparatus that can visualize interactions between molecules and molecular processes in biological cells (e.g., see figure 4, especially figure 4c-d wherein drug binding interactions were demonstrated for mitrozantrone in the nuclear inclusions).

For **claim 26**, Sharonov et al. disclose “the same” marker molecules (e.g., see figure 4 wherein mitrozantrone is shown in both the nuclear membrane and in the cytoplasm, DNA-bound mitrozantrone is also shown; see also maintained 35 U.S.C. 112, second paragraph rejection).

For **claim 27**, Sharonov et al. disclose different marker molecules (e.g., see figure 4 wherein both “bound” and “unbound” mitrozantrone are shown; compare also figures 4-5 wherein both doxorubicin and mitrozantrone are used; see also figure 1; see also maintained 35 U.S.C. 112, second paragraph rejection).

For **claim 28**, Sharonov et al. disclose adjusting the wavelength during use from 457.9 to 514.5 nm (e.g., see page 42, column 2, paragraph 1).

For **claims 30 and 64**, Sharonov et al. disclose in addition to the arrangement of claim 24  $20\text{ }\mu\text{m} \times 20\text{ }\mu\text{m} = 400\text{ }\mu\text{m}^2$  (e.g., see Sharonov et al., page 42, column 1, last paragraph).

For **claims 31 and 67**, Sharonov et al. disclose a control unit that is adapted to coordinate and synchronize positioning and shifting of images to each sample position on

a pixel array of said CCD camera (e.g., see page 41, column 2, second to last paragraph; see also page 42, column 2, paragraphs 2-3; see also page 43, column 1, paragraph 2).

For **claims 33-34**, Sharonov et al. disclose an acousto-optically switchable laser (e.g., see figure 2, element 1; see also page 42, paragraph bridging columns 1-2 wherein a switchable Spectra-Physics Model 2026 is disclosed).

9. Claims 24, 26, 27, 30, 32, 34, 35, 37, 61, 62, and 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.; Xie, S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, 101(38) 7019-7023) (10/23/03 IDS, Reference C8).

For **claims 24 and 62**, Sanchez et al. (see entire document) disclose an apparatus for room temperature fluorescence imaging and spectroscopy of single molecules by two-photon excitation, which anticipates the claimed invention (e.g., see abstract; see also figure 1). For example, Sanchez et al. disclose at least one source of light configured for large-area fluorescence, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see figure 1 wherein Argon Ion laser is disclosed; see also Experimental section, paragraph 1 wherein a Ti-sapphire "two-photon" excitation laser is disclosed). Sanchez et al. do not explicitly state that the light source is adapted for large-area fluorescent excitation, but the Examiner contends that this would be an inherent property of the laser because Applicants' most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, "only

the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser"; see also claims 32 and 34; see also page 13 of Applicant's specification wherein the method of Sanchez was disclosed as a preferred embodiment) (emphasis added). Moreover, Sanchez et al. disclose the excitation of a  $10 \times 10 \mu\text{m}^2$  region =  $100 \mu\text{m}^2$  (e.g., see Sanchez et al., page 42, column 1, last paragraph), which falls within Applicants' most preferred range of 100 to 10,000  $\mu\text{m}^2$  (e.g., see specification, page 7, middle paragraph, "the large-area fluorescence excitation, preferably 100 to 10,000  $\mu\text{m}^2$ , depending on the application"; see also 35 U.S.C. § 112, second paragraph rejection below). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term "large-area" fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, Sanchez et al. disclose a sample holder (e.g., see figure 1 wherein the sample holder is labeled). Sanchez et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see figure 1 wherein the CCD camera is labeled; see also page 7021, column 2, last paragraph; see also Experimental section wherein a Nikon Diaphot 300 inverted epifluorescent microscope is disclosed). Sanchez et al. disclose a detection and analysis system wherein at least one of the sample

holder and the detection and analysis system is moveable laterally, relative to the other during use (e.g., see figure 1 wherein XY scanbed is disclosed). Finally, Sanchez et al. disclose a control unit adapted to coordinate and synchronize illumination times and lateral movement between said sample holder and said detection and analysis system during use (e.g., see Experimental Section, last paragraph, wherein “a modified Nanoscope IIIA controller was used for controlling the scan bed and image acquisition”; see also figure 1).

Sanchez et al. do not explicitly state that said arrangement has been “adapted” to visualize movements of molecules, interactions between molecules, and molecular processes in a sample during use, by using a single dye tracing (SDT) method. However, the Examiner contends that Sanchez et al. inherently discloses this limitation (e.g., see Sanchez et al., Results and Discussion; see also figure 2). For example, Sanchez et al. teach an arrangement that can image a single dye molecule (e.g., see Sanchez et al., abstract). Thus, Sanchez et al. teach the visualization of the movements of molecules (e.g., see Sanchez et al., page 7020, “Each peak in Figure 2 is due to a single molecule, evidenced by the abrupt disappearance of the signal in the subsequent images [i.e., the movement of single molecules and/or lack thereof can be ascertained via subsequent images using this technique]”), interactions between molecules (e.g., see Sanchez et al., figure 2 wherein interactions between individual RHB dye molecules and individual RHB dye molecules and the substrate surface can be seen in this and subsequent images) and molecular process in a sample during use (e.g., figure 2; see also Each peak in Figure 2 is due to a single molecule ... The variation in intensities of the molecules are due to

different molecular orientations”; see also page 7019, paragraph bridging columns 1-2, “There have been tremendous developments in recent years of detection, imaging and spectroscopy of single molecules ... All these advance4s have resulted in a paradigm for studying mane single molecule behaviors , e.g., translational and rotational diffusion [e.g., examples of molecular processes] ... etc.”). Furthermore, Sanchez et al. disclose the use of a single dye tracing method (e.g., see Sanchez et al., abstract, “We report fluorescence imaging of single dye molecules ...”). “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term “large-area” fluorescence (e.g., see 35 U.S.C. § 112, second paragraph rejection below).

In addition, the Examiner argues in the alternative that Applicants’ “adaptation” element (i.e., see claim 24, last three lines) represents “intended use” language and thus is not afforded any patentable weight. Claims directed to apparatus must be distinguished from the prior art in terms of structure rather than function (e.g., see *In re Danly*, 263 F.2d 844, 847, 120 USPQ 528, 531 (CCPA 1959). “[A]pparatus claims cover what a device is, not what a device does.” *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469, 15 USPQ2d 1525, 1528 (Fed. Cir. 1990). (emphasis in original). A

claim containing a “recitation with respect to the manner in which a claimed apparatus is intended to be employed does not differentiate the claimed apparatus from a prior art apparatus” if the prior art apparatus teaches all the structural limitations of the claim. Ex parte Masham, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicant’s claim language only sets forth what the apparatus does (i.e., adapted to visualize movements of molecules ... using a single dye tracing (SDT) method) rather than what it is (i.e., describe a structural limitation) and, as a result, fails to distinguish the claimed apparatus from the prior art in terms of its structure. Furthermore, it is even if *assuming arguendo* this “adaptation” is to be afforded patentable weight, the Examiner contends that the metes and bounds of the claimed invention cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph below).

For **claim 26**, Sanchez et al. disclose, for example, “the same” RhB dye marker molecules (e.g., see Figure 2)

For **claim 27**, Sanchez et al. disclose do not disclose the use of “different marker molecules, but this limitation has not been given any patentable weight because it represents intended use only. If the prior art structure is capable of performing the intended use, then it meets the claim. The Office does not have the facilities to make a comparison and the burden is on the applicants to establish any difference between the transducing elements of the art and the instant claims. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

For **claims 30 and 64**, Sanchez et al. disclose in addition to the arrangement of

claim 24,  $10 \times 10 \mu\text{m} = 100 \mu\text{m}^2$  (e.g., see Sanchez et al. page 7022, column 2, paragraph 1).

For *claims 32 and 34*, Sanchez et al. disclose, for example, an argon laser and/or a “two-photon” excitation laser (e.g., see figure 1; see also Experimental section).

For *claim 35*, Sanchez et al. disclose a control unit that further comprises a pulse transmitter and a software adapted to control said at least one source of light and said movement of said sample holder during use (e.g., see Sanchez et al., figure 1; see also Experimental section, paragraph 3, wherein Nanoscope IIIA controller is used for “controlling the scan bed and image acquisition”; see also paragraph 1 wherein 100 fs pulses are disclosed).

For *claim 37*, Sanchez et al. disclose an inverted epifluorescence microscope (e.g., see Experimental section).

For *claim 61*, Sanchez et al. disclose lateral movement (e.g., see figure 1, XY scanbed).

### ***Response***

10. Applicant’s arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants’ newly amended and/or added claims and/or arguments.

[1] Applicants argue, “Sharonov and Sanchez do not teach ‘a light source



configured for use in large-area fluorescent excitation' ... because Sharonov and Sanchez are directed solely to confocal microscopy ... [which] is completely different from the large-area fluorescent excitation technique recited by the present claims ... as established by the declaratory evidence previously submitted by Applicant, persons of ordinary skill in the art understand that large-area fluorescent excitation does require the use of simultaneous excitation ... [and, as a result] Sharonov and Sanchez do not teach a light source configured for use in large-area fluorescent excitation" (e.g., see 12/22/06 Response, page 14, section 1).

[1] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a limitation excluding "confocal" microscopy) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, the claims recite "large-area fluorescent excitation", not "non-confocal" microscopy techniques. The declarant sets forth references that do not even mention the term "large-area fluorescent excitation" and thus these references cannot be relied upon to prove its meaning. In addition, the office has provided several references (Li and Yelin) demonstrating that large areas can be viewed using confocal techniques either by tiling (e.g., Li et al.) or using a single scan (e.g., see Yelin, page 1102, column 2, paragraph 2, SECM was previously demonstrated with a  $440\mu\text{m} \times 400\mu\text{m}$  field of view"; see also Li et al. reference citation above). Claims are to be given their broadest reasonable interpretation consistent with Applicants' specification

(e.g., see *In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111. Here, confocal microscopy can be used to view large areas including areas within the claimed 100 to 10,000  $\mu\text{m}^2$  (e.g., see claim 30) and thus use of references that teach confocal microscopy is not inconsistent with Applicants' claims and/or specification. In addition, "large-area" is a relative term wherein the metes and bounds of the claimed scope cannot be determined (see 35 U.S.C. § 112, second paragraph rejection above).

[2] Applicants argue, "neither Sharonov nor Sanchez teaches a control unit adapted to coordinate and synchronize illumination times and lateral movement ... The Federal Circuit has afforded patentable weight to elements 'adapted to' perform a function. See, e.g., *Pac-Tec, Inc. v. Amerace Corp.*, 903 F.2d 796, 801 (Fed. Cir. 1990). ... The control unit of the present claims is described in the articles "Ultra-sensitive DNA Detection on Microarrays" ... and "A fast Scanner for Fluorescence Microscopy Using a 2-D CCD and Time Delayed Integration" ... which describe the control unit of the present claims as operating in time delayed integration (TDI) mode. That the control unit of the present claims is adapted for operating in TDI mode is also disclosed in the present specification at pp. 8-9 ("the control unit can also coordinate and synchronize the positioning and the shifting of the images to each sample position on the pixel array of the CCD camera and control and coordinate the readout and the evaluation of the pixel array images"). Neither Sharonov nor Sanchez discloses a control unit adapted to operate a CCD camera in TDI mode ... nor do they disclose that the TDI mode is used for controlling a sample holder." (e.g., see 12/22/06 response, pages 14 and 15).

[2] Again, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., time delayed integration) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the event that Applicants' "adapted to" limitation is to be afforded patentable weight it is noted that the time delayed integration limitation is not recited in Applicants' claims. Thus, Applicants' claims are not limited to such control units.

[3] Applicants argue, "Sharonov merely states, "The scanning of the sample stage and minors of the optical scanner and all operations connected with recording of spectra are computer-controlled ... A disclosure that scanning operations are 'computer-controlled; does not amount to the teaching of a controller adapted to coordinate and synchronize illumination times and lateral movement." (e.g., see 12/22/06 Response, page 15, last paragraph).

[3] The Examiner respectfully disagrees. The term "adapted to" if it is to be afforded patentable weight would only require that the device be structurally "capable" of performing the function (e.g., see, *In re Venezia*, 530 F.2d 956, 959, 189 USPQ 149, 151-52 (CCPA 1976)), which a computer certainly would be "capable" of doing (i.e., it could be programmed to do so and thus inherently possesses this capability).

[4] Applicants argue, "[with regard to Sanchez] the disclosure that a "controller" was used for controlling the scan bed and image acquisition does not amount to the

teaching of a controller adapted to coordinate and synchronize illumination times and lateral movement.” (e.g., see 12/22/06 Response paragraph bridging pages 15 and 16).

[4] Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants set forth the general allegation that Sanchez “does not amount to the teachings of a controller [as claimed]” but fail to state why this is the case.

[5] Applicants argue, “neither Sharonov nor Sanchez teaches an arrangement that is adapted to visualize movements of molecules by using a single dye tracing (SDT) method.” (e.g., see 12/22/06 Response, page 16, section 3).

[5] The cited phrase is indefinite (e.g., see 35 U.S.C. § 112, second paragraph rejection above) and, as a result, Applicants’ arguments are moot. For example, Gensch et al. disclose that commercially available, unmodified confocal microscopes possess both the power and resolution to examine single molecules (e.g., see Gensch et al., figure 2 and experimental section) and thus it unclear what further modification would be required when any commercially available microscope will do.

#### ***Claim Rejections - 35 USC § 103***

11. Claims 24, 26, 27, 29, 30, 32, 34, 35, 37, 44, 61, 62, and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez et al. (Sanchez, E. J.; Novotny, L.; Holtom, G. R.;

Xie, S. "Room-Temperature Fluorescence Imaging and Spectroscopy of Single Molecules by Two-Photon Excitation" *Journal of Physical Chemistry A* **September 18, 1997**, 101(38) 7019-7023) (10/23/03 IDS, Reference C8) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**).

For *claims 24, 26, 27, 30, 32, 34, 35, 37, 61, 62, 64*, Sanchez et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates and, as a result, renders obvious claims 24, 26, 27, 30, 32, 34, 35, 37, 61, 62, 64.

The prior art teaching of Sanchez et al. differs from the claimed invention as follows:

For *claim 29*, the prior art teachings of Sanchez et al. differ from the claimed invention by not specifically reciting the use of both horizontal (x and y direction) and vertical (z direction) control.

For *claim 44*, the prior art teachings of Sanchez et al. differ from the claimed invention by not reciting the use of a piezo element.

However, Lewis et al. teach the following limitations that are deficient in Sanchez et al.:

For *claim 29*, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For **claim 44**, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, “Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously”).

It would have been obvious to one skilled in the art at the time the invention was made to use the fluorescence imaging and spectroscopy apparatus as taught by Sanchez et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their “flat design” is “particularly well suited for ... confocal optical microscopy” (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Sanchez et al. (e.g., see Sanchez et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state that their invention is “ideally suited for stage scanning confocal optical microscopy. Its inherent axial positioning capability provides a mechanism for optically slicing sample in the z direction while scanning it through the confocal spot” (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4, “The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective”). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes and especially with confocal

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microscopy disclosed by Sanchez (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, "Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes").

### *Response*

12. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues, "As explained in detail above (with regard to Sanchez) and in the previous Responses (with regard to Sanchez and Lewis), the cited references do not teach all of the limitations of the rejected claims. Neither Sanchez nor Lewis teaches (1) a light source configured for use in large-area fluorescent excitation, or (2) a control unit adapted to coordinate and synchronize illumination times and lateral movement. For at least these reasons, a prima facie case of obviousness has not been established." (e.g., see 12/22/06 Response, pages 16 and 17, especially page 17, paragraph 1).

To the extent that Applicants are merely repeating their previous arguments with regard to Sanchez and/or Lewis alone, the Examiner contends that those issues were adequately addressed in those previous sections.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

13. Claims 24, 26-40, 42, 44, 45, 61, 62, and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (Schmidt, T. H.; Schutz, G. J.; Baumgartner, W.; Gruber, H. J.; Schindler, H. "Imaging of single molecule diffusion" PNAS 1996, 93, 2926-2929) (of record) and Lewis et al. (U.S. Patent No. 5,705,878) (Date of Patent is **January 6, 1998**) as evidenced by Schmidt et al. (Schmidt, T. H.; Hinterforfer, P.; Schnidler, H. "Microscopy for Recognition of Individual Molecules" *Laser und Optoelektronik* **1997**, 29(1), 56-62) (referred to herein as "Schmidt 1997") and Albertine et al. (e.g., see Albertine, K. H.; Cerasoli, F.; Gee M. H.; Ishihara, Y.; Tahamont, M. V.; Gottlieb, J. E.; Peters, S. P. "Morphological analysis of the activation of adherent neutrophils in vitro" *Tissue Cell* **1998** 20(4), 519-530) and Al-Ghoul et al. (Al-Ghoul, K. J.; Costello, M. J.; "Light Microscopic Variation of Fiber Cell Size, Shape and Ordering in the Equatorial Plane of Bovine and Human Lenses" *Molecular Vision* 1997, 3, 2).

For *claims 24 and 62*, Schmidt et al. (see entire document) teach a method for imaging single molecule diffusion (e.g., see Schmidt et al., abstract), which reads on the claimed invention. For example, Schmidt et al. teach the use of at least one source of light configured for large-area fluorescent excitation, via single or multiple photon absorption, of marker molecules in said sample during use (e.g., see Schmidt et al., page 2926 wherein an argon-laser is disclosed, "For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera"; see also figure 1). In addition, Schmidt et al. teach a sample holder (e.g., see page 2927, column 1, paragraph 2 wherein samples are immobilized on a



cover-slip). Schmidt et al. also disclose a detection and analysis system comprising a charged coupled device (CCD) camera (e.g., see Schmidt et al., page 2926 wherein an epifluorescence microscope equipped with a nitrogen-cooled CCD camera is disclosed, “For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera”). Finally, Schmidt et al. disclose a control unit adapted to coordinate and synchronize illumination times (e.g., see Schmidt et al., page 2926-2927 wherein a CCD camera equipped with a TH512B chip is disclosed “... provid[ing] trigger pulses for the acousto-optic modulator for repeated illuminations”). Schmidt et al. also disclose an arrangement adapted to visualize movements of molecules, interactions between molecules, and molecular process in a sample during use (e.g., see Schmidt et al., abstract, “Here we provide methodology for visualization of the motion of individual fluorescent molecules”; see also figures 1 and 3 showing interaction of individual lipid with other lipids in the membrane).

For **claim 25**, Schmidt et al. disclose the use of biological cells (e.g., see Schmidt et al., page 2929, Conclusion).

For **claims 26-27**, a recitation directed to the manner in which a claimed apparatus is intended to be used does not distinguish the claimed apparatus from the prior art – if the prior art has the capability to so perform. See MPEP 2114 and *Ex parte Masham*, 2 USPQ2d 1647 (Bd. Pat. App. & Inter. 1987). Here, Applicants use of equal or different markers does not impart any patentably distinct features on the apparatus and thus is not given any patentable weight in accordance with MPEP § 2114. However, even if

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assuming arguing the use of said sample markers were to be given patentable weight, Schmidt et al. disclose both equal and different marker molecules (e.g., Materials and Methods section wherein equal TRITC DHPE molecules are disclosed; see also bell curve in figure 2 showing some “markers” with less than 100 counts and some with greater than 300 counts i.e., different markers; see also Conclusion wherein different markers are disclosed).

For **claim 28**, Schmidt et al. disclose the coordination and synchronization of 5 ms Gaussian-shaped laser beam pulses of 6.1  $\mu\text{m}$  width and 57 kW/cm<sup>2</sup> mean excitation intensity taken at 35 ms intervals (e.g., see figures 1 and 3).

For **claims 30 and 64**, Schmidt et al. do not explicitly state that their laser will excite a range from 100 to 10,000  $\mu\text{m}^2$ , but the Examiner contends that this level of excitation would be an inherent property of the laser because Applicants’ most preferred embodiment for large-area fluorescent excitation is a laser (e.g., see specification, page 7, middle paragraph, “only the source of light needs to be suitable for large-area fluorescence excitation. Here, a preferred source of light is a laser”; see also claim 32) (emphasis added). “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). In addition, it is not clear what is meant by the term “large-area” fluorescence (e.g., see 35

U.S.C. § 112, second paragraph rejection below).

For **claims 31 and 67**, Schmidt et al. disclose positioning and shifting of images using a “frameshift” CCD camera equipped with both (1) acquisition and (2) storage functional capabilities and the ability to “synchronize” and “coordinate” between these two functions.

For **claims 32 and 34**, Schmidt et al. disclose an argon-ion laser (e.g., see Schmidt et al., page 2926, column 1, paragraph 1).

For **claim 33**, Schmidt et al. disclose an acousto-optically switchable laser light (e.g., see Schmidt et al., page 2927, column 1, paragraph 1, “The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations”).

For **claim 35**, Schmidt et al. disclose a pulse transmitter and mechanism for controlling said transmitter wherein the laser can generate 5 ms pulses (e.g., see Schmidt et al., Materials and Methods section; see also page 2927, column 1, paragraph 1, “The camera provided trigger pulses for the acoustoptic modulator for repeated illuminations”).

For **claims 36 and 68**, Schmidt et al., disclose both “continuous” and “frameshift” CCD modes (e.g., see Schmidt et al., page 2926, column 2, last paragraph).

For **claim 37**, Schmidt et al., disclose an epifluorescence microscope (e.g., see page 2926, column 1, last paragraph, “For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera”; see also Materials and Methods section).

For **claim 38**, Schmidt et al. disclose and efficiency of 3% (e.g., see Schmidt et

al., page 2926, column 1, last paragraph).

For **claim 39**, Schmidt et al. disclose a N<sub>2</sub> cooled CCD camera with a large pixel array and noise of only a few electrons per pixel (e.g., see page 2926, column 1, last paragraph, “For this, we used epifluorescence microscopy with argon-ion laser excitation and imaging onto a highly-sensitive liquid-nitrogen-cooled CCD-camera”; see also Materials and Methods section wherein 4 counts/pixel read-out noise is disclosed). Schmidt et al. do not disclose the quantum efficiency or dark counts of their SDT system. The reference is silent on the issue. However, the Examiner contends that these features would be an inherent property of the system as disclosed by a later paper by Schmidt et al. (referred to herein as “Schmidt 1997”) referring back to the previous studies (e.g., see Schmidt 1997, translation, page 7, Figure 1B shows the setup for single molecule detection with a conventional epifluorescence microscope and a nitrogen-cooled CCD camera (4cnts readout noise, dark counts negligible, quantum efficiency 0.8 electrons/photon”); please note that reference [12] refers to the previous Schmidt et al. article published in 1996).

For **claim 45**, Schmidt et al discloses the same Axiovert 135-TV Zeiss microscope as that disclose in Applicant’s preferred embodiments (e.g., see Example 1 in Specification) and, as a result, must possess the same parallel beam region. “When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the

difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

The prior art teachings of Schmidt et al. differ from the claimed invention as follows:

For **claims 29, 35, 65 and 66**, Schmidt et al. are deficient in that they do not specifically teach the use of an XYZ stage for automated lateral and vertical movements. Schmidt et al. is silent on the issue.

For **claim 40**, Schmidt et al. are deficient in that they do not teach the use of a pixel array  $> 1340 \times 1300$ .

For **claim 42**, Schmidt et al. are deficient in that they do not teach the use of a microtiter plate.

For **claim 44**, Schmidt et al. are deficient in that they do not teach the use of a piezo element used in conjunction with the XYZ stage for Z moments.

However, the combined references of Lewis et al., Al-Ghoul et al. and Albertine et al. teach the following limitations that are deficient in Schmidt et al.:

For **claims 29, 35, 65 and 66**, Lewis et al. (see entire document) teach that x, y and z control using an automated flat scanning stage (e.g., see Lewis et al., Summary of the Invention; see also column 3, lines 24-28, "Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously"; see also figures 1-4).

For **claim 40**, Al-Ghoul et al. teach the use of a pixel array that is  $2048 \times 2048$

(e.g., see page 2, column 2, paragraph 2).

For **claim 42**, Albertine et al. teach the use of a microtiter plate for use in microscopy of biological samples for “parallel” screening and identification (e.g., see Albertine et al., abstract).

For **claim 44**, Lewis et al. teach the use of a piezo element (e.g., see Lewis et al., Summary of the Invention; see also figures 1, 2 and 4; see also column 3, lines 24-28, “Lateral (X-Y) scanning of frame 30 is performed by using the piezo tubes in pairs while axial positioning in a direction (Z) perpendicular to the X,Y plane is provided by using all four tubes simultaneously”).

It would have been obvious to one skilled in the art at the time the invention was made to use the single dye tracing apparatus as taught by Schmidt et al. with the automated flat scanning XYZ stage as taught by Lewis et al. because Lewis et al. explicitly states that their “flat design” is “particularly well suited for ... microscopy” (e.g., see Lewis et al., column 1, lines 11-14), which would encompass the confocal microscopy apparatus disclosed by Schmidt et al. (e.g., see Schmidt et al., Introduction). Furthermore, one of ordinary skill in the art would have been motivated to use the piezo XYZ stage disclosed by Lewis et al. because Lewis et al. explicitly state, “The principle advantage of the present scanner over previous geometries is that the three-dimensional scanning is accomplished in a flat thin plate which can be readily placed close to a high power microscope objective” (e.g., see Lewis et al., column 2, lines 40-45; see also paragraph bridging columns 3-4), which would encompass the microscope objective disclosed by Schmidt et al. Furthermore, one of ordinary skill in the art would have

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reasonably expected to be successful because Lewis et al. teach that their stage is compatible with all types of microscopes (see Lewis et al., Summary of Invention; see also column 4, paragraph 1, “Since the scanner does not extend below the plane of the plate, the objective is completely free to be exchanged by the simple rotation mechanisms found in all optical microscopes”).

In addition, a person of skill in the art would have been motivated to use the microtiter plates disclosed by Albertine et al. with the single dye tracing apparatus as disclosed by Schmidt et al. because Albertine et al. explicitly states that their microtiter plates can be used with microscopy (e.g., see Albertine et al., abstract). Furthermore, a person of skill in the art would have been motivated to use a microtiter plate to prepare and/or test samples in “parallel” i.e., to save time. Furthermore, a person of skill in the art would have reasonably been expected to be successful because Albertine et al. show that microtiter plates can be used in conjunction with microscopes.

Finally, a person of skill in the art would have been motivated to use the  $2048 \times 2048$  pixel array to replace the smaller arrays disclosed by Schmidt et al. because this array is designed to collect images in the same manner as the smaller arrays (i.e., the references represent analogous art). A person of skill in the art would have been motivated to use the array disclosed by Al-Ghoul et al. because it possesses higher resolution (i.e.,  $2048 \times 2048$ ). A person of skill would have reasonably been expected to be successful because the array is used in a CCD camera just as is the case for Schmidt et al.

***Response***

14. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from its original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicant argues, "As explained in the previous Response, Schmidt-1 does not teach a control unit adapted to coordinate and synchronize illumination times and lateral movement between a sample holder and a detection and analysis system during use ... once again does not even assert that Schmidt-1 teaches a control unit adapted to coordinate and synchronize illumination times and lateral movement, instead merely arguing that Schmidt-1 teaches 'a control unit adapted to coordinate and synchronize illumination times.'" (e.g., see 12/22/06 Response, page 17).

[1] In response to applicant's arguments against the Schmidt-1 reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combination of references teaches all the claimed limitations including the control unit as set forth in the above rejection.

[2] Applicants argue, "The Office's assertion that the limitation "a control unit adapted to coordinate and synchronize illumination times and lateral movement" does not



constitute a limitation in any patentable sense lacks merit.” (e.g., see 12/22/06 Response, paragraph bridging pages 17 and 18).

[3] Applicants argue, “An explanation of the differences in the sequential recording system of Schmidt-1 and the TDI system of the present claims is found in the article "Single-Molecule Reader for High- Throughput Bioanalysis" by Hesse, et al., Anal.Chem. 76 (2004):5960-5964 ("Hesse-3") (attached hereto as Appendix C). The system of Schmidt-1 is described therein as a "conventional microscope-based system" that acquires sequential images in order to cover large areas. Hesse-3, p. 5960, col. 2. With sequential recording devices such as the one in Schmidt-1, inertia of the moving parts requires time-consuming feedback loops for precise stops, limiting the overall readout speed. Id. at p. 5961, col. 1. In contrast, the system of the present claims is described as "a scanning system that avoids overhead times due to both stage positioning and illumination, based on the implementation of synchronized continuous stage-shift and camera readout." Id. The system of the present claims achieves this effect by operating the camera in TDI mode. Id. None of the cited references discloses a control unit adapted to operate a CCD camera in TDI mode” (e.g., see 12/22/06 Response, page 18).

[3] In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (e.g., TDI mode) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into

the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

[4] Applicants argue, “a visualization of single molecules during movement is not possible, particularly because the sample movement in Schmidt-1 only measures on very small areas (1 1 x 1 pm<sup>2</sup>)” (e.g., see 12/22/06 Response, page

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

### **New Rejections**

#### ***Claims Rejections - 35 U.S.C. 112, first paragraph***

15. Claim 63 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claim 63 was added in the 12/22/06 Response. However, the specification fails to provide support for the currently claimed “wide-field” limitation in line 2. The doctrine of claim differentiation creates a presumption that each claim in a patent has a different scope. *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998). “There is presumed to be a difference in meaning and scope when different words or phrases are used in separate claims. To the extent that the absence of such difference in meaning and scope would make a claim superfluous, the doctrine of claim differentiation states the presumption that the difference between claims is significant.” *Id.* at 1005. Here, claim 63 would be superfluous relative to claim 24 if

“large area fluorescent excitation” and “wide field illumination” were equivalent. Thus, the change in scope going from “large area fluorescent excitation” to “wide field illumination” represents new matter (e.g., wide-field creates a new subgenus drawn only to non-confocal techniques whereas “large-field” was not so limited, see 35 U.S.C. § 112, second paragraph rejection above and responses thereto). Therefore, claim 63 and all-dependent claims are rejected for containing new matter.

### *Conclusion*

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.  
June 14, 2007

JON EPPERSON  
PRIMARY EXAMINER

